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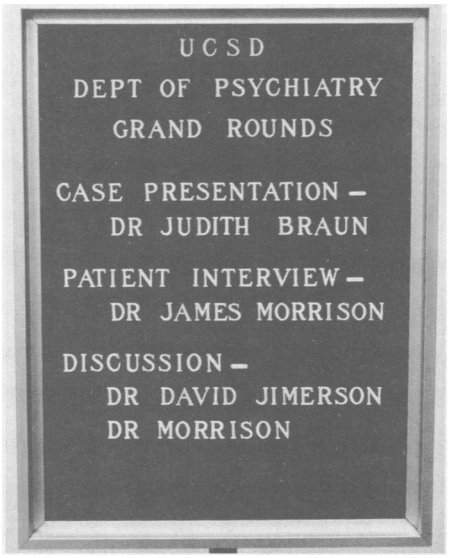

Anxiety Neurosis, Depressive Disorder and Meprobamate Addiction

Based on Psychiatric Grand Rounds held at the San Diego Veterans Administration Hospital, a teaching facility of the School of Medicine, University of California, San Diego, in late 1973; edited by Barbara Blomgren, BA, and Leighton Huey, MD.

DR. BRAUN:* Janet Hull† was brought to the emergency room four months ago with complaints of fatigue, weakness and inability to do her housework for about six months. Mrs. Hull, who is 47 years old, has been married to the same man for 27 years, and they have eight children. Her husband is a contractor; she has trained herself to keep the company books, and together they have built a substantial business near Los Angeles. Although this was the first time she had been seen by a psychiatrist, Mrs. Hull had gone to other hospital emergency rooms complaining of palpitations, tingling and shortness of breath about ten times in the past 28 years and had been treated successfully with diazepam for what were called anxiety attacks.

Mrs. Hull had borne six children before she began thinking of limiting her family. When her fifth child was born by cesarean section she realized that she would need surgical operation for any future deliveries. Her seventh child was conceived while she was taking norethynodrel and mestanol. After that child was born she asked for a tubal ligation, but local hospital rules forbade it. Although her eighth child was initially unwanted, Mrs. Hull claims that as her pregnancy progressed she began to look forward to the birth. A boy was born healthy and without problems, and Mrs. Hull was granted a tubal ligation. At first she denied any sorrow about her sterilization, but recently she has spoken of the grief she felt. She did not want more children, but she missed the possibility of being able to be a mother again. She cared for her eighth baby without difficulty and apparently did not withdraw from him, but she says that her weakness and fatigue began around the time of his birth six years ago. She pushed on with her extensive household and accounting duties, arising each morning around two o'clock in order to accomplish everything. In addition to the six children still at home, she cared for her mother, who lives with her.

About four years ago Mrs. Hull began seeing her family physician about her fatigue and malaise. Findings on repeated physical and serological ex-

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†The patient's name is fictitious.

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aminations showed no organic source for her fatigue. She complained of difficulty getting to sleep at night and was given a prescription for meprobamate (Equanil®), which she claims helped her to get to sleep but did not affect her fatigue. She returned to her doctor many times during the four years.

About a year ago the family noticed a definite change in Mrs. Hull. She had more and more difficulty getting her housework and accounting done. She had to be coaxed to eat, and she lost 20 to 30 pounds the six months before admission to hospital. Her insomnia persisted; she continued to take meprobamate, claiming to take only three tablets a day. Her mother became ill with cancer of the cervix, and Mrs. Hull feels she did take good care of her mother during that illness despite her own fatigue. Her family says that Mrs. Hull was chronically pale and listless. She was often slightly ataxic in the morning and would return to bed. She denies being alarmed by her weakness, but her husband says that she was constantly worrying about dying and leaving him with all the responsibilities. She began worrying about their marriage and accused her husband of having affairs, which he emphatically denies. Both the Hulls claim that their sexual relationship has been undisturbed by her fatigue. Mrs. Hull's menstrual periods have continued to be regular. She has mentioned no suicidal thoughts and says that she has not had hallucinations.

She has not abused alcohol or drugs except for the chronic ingestion of meprobamate. About three weeks before admission she was stopped by the police for erratic driving and was ataxic when she got out of her car. The blood level of meprobamate was 4.2 mg per 100 ml. After that incident she was embarrassed and withdrew to her bed. Either her husband or her sister-in-law, who is a nurse, stayed with her day and night for two weeks. They are convinced that she took no medication at all during that time, and she had no ill effects from that apparent withdrawal of meprobamate.

Mrs. Hull was born in the Southwest, the second of two daughters. When she was about 12 years old her mother had an affair with an employee of her father. The sister eventually told the father about this, and the parents separated. A couple of years later, unable to tolerate living with their mother and her lover, the girls set out on their own, traveling, working and sometimes attending school. Mrs. Hull describes that period of her life as lonely and frightening. She completed high school, took some courses in business college and joined the Women's Army Corps for a time during World War II. She dated infrequently and decided to marry her husband after knowing him for only 19 days. She has had no other sexual relationships.

Shortly after their marriage, Mrs. Hull's sister died of a pulmonary embolism secondary to a cesarean section. Mrs. Hull grieved deeply and often thinks of her sister on the anniversary of her death. Although she had considerable anger toward her mother, Mrs. Hull felt that she ought to take care of her, and her mother came to live with her more than ten years ago. The mother is described by the family as a morbid person, and Mrs. Hull says she is very cold and aloof; she does not remember her mother kissing her, even in childhood.

When Mrs. Hull was admitted to the hospital she was emaciated and looked far older than 47. Lying in bed, she responded appropriately to questions and became tearful as she was discussing how much she *should* do and how much she was *unable* to do. During the physical examination she kept her arms around my waist, not wanting to let go. She was oriented to place and person, but not to time. She changed her history several times, and she refused to do calculations. She forgot details of a story I told her, but she was able to recite five digits forward and four digits backward without error. I found no evidence of a formal thought disorder. She was very concerned about abandonment and death. She was afraid that if she went to sleep she would not wake in the morning. Her fear of her husband having affairs was the only evidence of delusional thinking. She had a fairly normal range of affect, with depressive qualities. Although she used a great deal of denial, she did recognize that she was ill in some way.

Findings on the physical examination were normal except for her refusal to stand for fear of falling. Results of pelvic, rectal and neurological examinations were normal. Laboratory studies—including lumbar puncture, brain scan, Papanicolaou smear and complete blood chemistry—showed no organic cause for the illness. Neurological and medical consultants also could find no evidence of organic disease.

Mrs. Hull was disoriented and confused at times during her first few days in hospital. When I learned from her husband that she had taken five

tablets of meprobamate immediately before coming to the hospital, I prescribed meprobamate (800 mg every day for five days and then 400 mg every day for five more days), taking into account that complete withdrawal had apparently been accomplished at home two weeks earlier without bad effects. Mrs. Hull integrated herself into our therapeutic community fairly rapidly. She was not tearful or afraid. On her sixth hospital day she had one major motor seizure and another that may have been a major motor seizure. The blood chemistry at that time was entirely normal. Findings on an electroencephalogram (EEG) the following day were indeterminant, and a tracing three days later showed a dysrhythmia Grade II. Neurologists felt that this represented an intrinsic focus, and was not the result of either drug ingestion or withdrawal. Because I interpreted her seizures as meprobamate withdrawal seizures I reinstituted the higher dose of the drug and, on the recommendation of neurologists, also prescribed phenobarbital and diphenylhydantoin.

After the seizures Mrs. Hull's behavior changed dramatically, becoming slightly hypomanic—with pressured speech, inability to sit still, extreme busyness and inability to listen. She became afaid that she would be sexually assaulted on the ward. One week after her seizures she discussed her sexual fears in a group therapy session. The possibility was raised that perhaps she was having sexual fantasies about the men on the ward; she denied this emphatically.

The following day a telegram arrived saying that her daughter was critically ill and that she should return home immediately. She showed the telegram to several people and departed the next day without telling anyone she was leaving. (She later told me that she sent the telegram to herself.) The family called me several hours later, and I encouraged them to bring her back. With much agitation and a show of force they managed to transport her back here.

On return she was given thioridazine (100 mg every day), and within a few days her behavior became much less agitated and more appropriate. She was less sexually preoccupied. She was concerned about the seizures and her addiction, and made several unsolicited promises to me never to take meprobamate again. Remaining another two weeks for withdrawal from meprobamate, she participated appropriately on the ward, although she would not take any psychological tests. At the time of discharge her affect had a full range, but she was still using denial about her home life and problems in her marriage.

I have continued to see Mrs. Hull for an hour every other week. We have dealt with her concept and expectations of herself. She is an industrious and intelligent woman. She agreed to get some help in her house and to satisfy some of her own needs. She discussed at length her feelings of obligation to her mother, toward whom she feels much anger. She felt left out of the business and the household because of her reduced responsibilities when she returned home from the hospital. She also felt that her husband did not like her to be assertive and was thinking of leaving her. In a joint session, it became clear that Mr. Hull was indeed threatened by his wife's assertiveness, but he denied having an affair and reaffirmed his love for her. They agreed that Mrs. Hull would become partially reinvolved in the business to increase her sense of belonging, and they promised to try to communicate more directly with one another.

Concerned about a recurrence of the depression that Mrs. Hull's meprobamate addiction and subsequent hypomania had masked, a month ago I prescribed amitriptyline hydrochloride (150 mg every day), and she has improved considerably. She is scheduled to have an EEG done within the next month, and on the neurologist's recommendation I have continued the diphenylhydantoin until then. Mrs. Hull is beginning to pull away from therapy, mentioning the six-hour round trip drive here every other week as a burden, and after the interview I would appreciate discussing where to go from here.

(The patient was escorted into the room and introduced to Dr. Morrison. The following was excerpted from their interview.)

DR. MORRISON:* Mrs. Hull, thank you for coming in and talking in front of this rather large group of people this morning.

Patient: Well, I'm glad to come.

DR. MORRISON: Good. Can you tell us a little about what brought you to the hospital several months ago?

Patient: Well, I guess I should start about six months prior to when I came to the hospital. That seemed to be the point that it all came to. Of course I had been taking Equanil through the doctor's prescription for seven years. I told the doctor that I didn't feel like it was doing me

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any good, and I just couldn't pinpoint why I wasn't feeling better, you know. The last six months I just seemed to drop down lower and lower. Of course I had lost a lot of weight. I have gained back quite a lot now, but I carried about 90 pounds when I was home. I was real thin . . . and real nervous.

DR. MORRISON: You had been taking Equanil for seven years. Why?

Patient: Well, it wasn't excessive really. I had trouble through a pregnancy that required I stay in bed for about 10 or 12 weeks. My doctor gave me the medicine to keep me from being so jittery, I guess, just lying in bed all day long, you know. And of course I had to go to the hospital three or four times in that period, and then after I had the cesarean he said to still take this, and that carried on from him to this other doctor. And of course I had stated to the doctor that I was quite nervous.

DR. MORRISON: In years gone by had you suffered from attacks of nervousness?

Patient: No, not really. I don't think any more than anyone else. Of course things sometimes would make me upset. You know, if I thought someone was ill—those sorts of things.

DR. MORRISON: I got the impression from Dr. Braun that every year or two you had had an attack of feeling nervous, when you had trouble breathing and had to go to the emergency room or to the doctor to get a shot.

Patient: Well, she did state that right, although it was mostly over the last five or six years that I'd come to the point that someone called the fire department for a resuscitator. Even that didn't seem to help; on two occasions I was sent to the hospital.

DR. MORRISON: I see.

Patient: But many, many times I was just lying there with my husband or someone looking out for me because I was breathing so fast. It was something I had no control over.

DR. MORRISON: You must have felt very weak at those times.

Patient: Yes. I just couldn't sit up.

DR. MORRISON: What would be your state of mind at a time like that?

Patient: Well, it wasn't that bad; I just was hoping that it would stop.

DR. MORRISON: Would you be fearful?

Patient: I guess I was the last two times, going to the hospital.

DR. MORRISON: Would you ever be afraid that you were about to die, for instance?

Patient: Oh, yes. It came to the point when the breathing was so bad that I didn't feel I could gather another breath.

DR. MORRISON: Would you get chest pain at those times?

Patient: No.

DR. MORRISON: Or did you ever notice that your heart seemed to skip beats or beat very fast?

Patient: Oh, yes. That was what it was doing.

DR. MORRISON: Would you perspire excessively at those times?

Patient: Um hum.

DR. MORRISON: And would you notice any numbness or tingling in your hands or feet or around your lips?

Patient: No, I don't remember that.

DR. MORRISON: When was the first time you had an attack like that?

Patient: Well, I would put it back 20 years. But it was never a thing that you concentrated on, you know. It was just something that would happen on occasion.

DR. MORRISON: How long would the attacks last?

Patient: If they were bad they would last maybe 12 hours.

DR. MORRISON: Did you have to stop your normal activities and just lie there and suffer, or what?

Patient: Well, when I had it at home I didn't go to the doctor; I'd just lie there till it stopped.

DR. MORRISON: Now, since your last child was born, do I understand correctly that you've had an increase in these attacks?

Patient: I guess so.

DR. MORRISON: Has a doctor ever told you that you have any kind of lung or heart disorder? Has anything physical been found to explain your attacks?

Patient: No. I have had rheumatic fever. My old doctor seemed to think it could come from the rheumatic fever, but he didn't say that it did.

DR. MORRISON: And in the last year, how often were you having these anxiety attacks?

Patient: Maybe once a week. It's hard to say.

DR. MORRISON: Would they last 12 hours or so?

Patient: Oh, no. Not always.

DR. MORRISON: I wonder if you might tell us how your spirits were during the six months before you entered the hospital.

Patient: I guess they were all right, except I did get depressed because I was feeling bad.

DR. MORRISON: Feeling bad in terms of being listless or tired?

Patient: Um hum. Or maybe disgusted.

DR. MORRISON: Did you ever feel so disgusted that you felt there was no use going on?

Patient: Oh, no. Never.

DR. MORRISON: Did you have crying spells?

Patient: Well, yes. It wouldn't be just because I was feeling blue. There were not too many. I mean, to be perfectly frank, it would be when the children were causing me a litle trouble or when my husband and I had a little rough time. That always upset me a lot.

DR. MORRISON: Do you think you were crying more in those last six months?

Patient: Um hum.

DR. MORRISON: I understand your appetite suffered to some extent. How long had it been poor?

Patient: For maybe ten years.

DR. MORRISON: And how long ago was it that you began to lose weight?

Patient: Well, that was more of a gradual thing. I guess after the last boy was born I lost down to about a hundred pounds or so.

MR. MORRISON: What sort of trouble were you having with your sleep?

Patient: Well, I dreamt a lot and woke up very often also. I was getting up very early—two or three o'clock in the morning.

DR. MORRISON: What did you do when you got up? Would you have lots of energy and get things done?

Patient: I really did. It was surprising.

DR. MORRISON: So your energy wasn't failing you?

Patient: No, it didn't seem to. In fact, you know I kept the books for my husband, and that's usually when I worked on them, in the morning. In fact I sort of enjoyed it.

DR. MORRISON: So you kept your interest in things pretty well up until—when?

Patient: I guess about 20 days before I came here.

DR. MORRISON: As I understand it, though, there was a difference for you of some kind last winter, when you took to your bed? Can you tell us something about that?

Patient: I guess it was around January that I started losing interest in the home—I never did in the children and my husband—just in the home and cooking. I just used to take off to bed as soon as supper was finished and go to sleep. I was just exhausted.

DR. MORRISON: And did you notice any change in your spirits at that time?

Patient: Yes, they were down.

DR. MORRISON: Were there times that you felt pretty good?

Patient: Well, like I said, early in the morning I really felt like doing something. But then these other times I really was pushing myself.

DR. MORRISON: Well, how are you feeling now? Are your spirits up to about where they ought to be?

Patient: I would say so, and my husband thinks so. He said in fact I'm getting kinda ornery.

DR. MORRISON: What does that mean?

Patient: He means that I can hold my own with him. He's a little stubborn.

DR. MORRISON: I see. So you're back in fighting form.

Patient: You have to be with him. I think he kinda overtook me there for a while, you know.

DR. MORRISON: Well, thank you again for coming in and subjecting yourself to this.

Patient: Well, that's all right. I mean I just told you everything I know to the best of my ability.

DR. MORRISON: You were very helpful.

Patient: Well, thank you.

(The patient was escorted from the room.)

DR. MORRISON: Apprehension and psychic tension occur in virtually all psychiatric conditions,[1] and therein lies a problem; anxiety can be both a symptom of illness and a syndrome. We refer to a syndrome of anxiety attacks as *anxiety neurosis* when the attacks are not associated with other psychiatric conditions or with physical conditions like heart or lung disease, or with fear-invoking situations. This venerable syndome has been known for at least 75 years and goes by a number of other names, including neurasthenia, neurocirculatory esthenia, effort syndrome, soldier's heart, and perhaps 15 more. In their classic study of anxiety neurosis, Cohen and White[2] estimate that the condition may be seen in as many as 5

percent of the general population, and that perhaps 10 percent of patients seen in a cardiologist's office suffer not from organic heart disease but from anxiety neurosis. In a recent study of psychiatric outpatients by Woodruff and co-workers[3] in St. Louis, 12 percent of 500 patients interviewed were diagnosed as having anxiety neurosis.

The mean age of onset is in the early twenties, and the diagnosis is untenable if the onset occurs past the age of forty. Twice as many women as men suffer from anxiety neurosis. The anxiety tends to come in discrete attacks, not necessarily precipitated by fear-invoking situations. The person feels that something terrible is about to happen, that she is about to die. A sine qua non of anxiety neurosis is shortness of breath, either difficulty in catching one's breath or rapid breathing such as Mrs. Hull reported. The attacks are often immobilizing. The patient may have to sit or lie down and be afraid to move a muscle. Other symptoms include palpitations of the heart, tremors, paresthesias, numbness or tingling in the extremities or around the mouth, and pronounced weakness. Depressive thoughts or symptoms of depression probably occur in five out of six of these patients.[4] In Woodruff's[3] experience half the patients with anxiety neurosis suffered from a secondary affective disorder.

The origin of the condition is not clear. Perhaps 15 percent of parents and siblings of patients with anxiety neurosis also suffer from it. Slater[5] found about 50 percent of monozygotic cotwins of probands with anxiety neurosis also received that diagnosis, whereas only about 4 percent of dyzygotic cotwins of probands were so affected. Moreover, in a study of separately reared monozygotic twins there was essentially no difference in the interclass correlation coefficients on a test of neuroticism, indicating that environment cannot be presumed to be the differentiating factor. There appears to be some genetic factor in the predisposition to neurotic symptoms in general and to anxiety neurosis in particular.

The course of anxiety neurosis is chronic and benign. On 20-year follow-up most patients still have some symptoms, but well over half of them experience little difficulty. Perhaps a quarter of patients on long-term follow-up have occasional difficulty participating in normal activities, but they usually work around this by altering their lives in subtle ways. Perhaps 15 percent of patients have severe symptoms and disabilities, and it remains to the physician to decide upon a course of action to help these people.

DR. JIMERSON:* In this case it might also be helpful to take a closer look at the drug of abuse. The synthesis of meprobamate was part of an effort about 20 years ago to develop less toxic drugs to replace the barbiturates in the treatment of tense and anxious psychoneurotic patients. Early animal studies suggested that meprobamate possessed, in addition to anticonvulsant and interneuronal blocking capabilities, a unique tranquilizing property that made treated animals tame and docile without sedation or autonomic or extrapyramidal side effects, and without interference with intellectual or motor performance.

Meprobamate was first introduced in 1955, and effective advertising campaigns supplemented the early clinical reports of almost magical reduction of anxiety. That first year sales totaled nearly 2 million dollars.[6] For some years, case reports and studies of uncritical design continued to present meprobamate as panacea. By 1962, however, Weatherall[7] noted that 80 to 90 percent of the reports were "unacceptable" research.

The three important clinical effects of meprobamate are psychophysiological reduction of anxiety, prevention of petit mal seizures (for which it is less effective than trimethadione—in fact, meprobamate may aggravate grand mal epilepsy or myoclonic seizures) and relaxation of muscle tension (for which it is also of dubious efficacy). In their review of the literature in 1971, Greenblatt and Shader[6] found that in only 5 of 26 controlled double-blind studies was meprobamate clearly more effective than placebo, and in only one of ten controlled double-blind studies was it clearly more useful than a barbiturate. Given the equivocal efficacy and significant side effects of meprobamate, they concluded that its widespread use is irrational.

According to Goodman and Gilman[8] it is difficult to differentiate clinically between meprobamate and the barbiturates; only careful pharmacological analysis shows distinctions. Meprobamate is absorbed readily from the gastrointestinal tract; blood levels reach a peak within one or two hours and fall slowly over ten hours or more. The principal route of excretion is through the kidneys —90 percent emerges as an oxidized metabolite or a glucuronide. Like the barbiturates, mepro-

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bamate can induce the microsomal enzymes involved in drug metabolism.

The most common side effect of meprobamate is sedation; drowsiness is common at the typical dose of 400 mg four times a day. Psychological testing has shown some impairment of learning after an 800 mg dose and definite impairment of learning, motor coordination and reaction time after 1,600 mg. Hypersensitivity reactions occur in about 2 percent of patients, especially in persons with a history of dermatological or allergic problems, appearing most commonly as urticarial or intensely pruritic maculopapular and erythematous skin rashes. Other side effects include shaking chills and fever, nausea, vomiting, syncope and hypotension (particularly in elderly patients). Meprobamate is the only psychotropic agent other than the phenothiazines and tricyclic antidepressants known to produce significant incidence of hematological complications; these include thrombocytopenia, acute nonthrombocytopenic purpura, agranulocytosis (from which some fatalities have been reported), aplastic anemia and pancytopenia.

As to the risk of overdose, meprobamate is clearly less dangerous than the barbiturates, and just as clearly more dangerous than the benzodiazepine tranquilizers. In 1963, for example, psychotropic drugs were dispensed in approximately 46 million prescriptions; in that year there were 2,000 deaths from barbiturate overdoses and 79 from other psychotropic drug overdoses. The literature as of 1970 contained no cases of fatal poisoning by chlordiazepoxide, diazepam or oxazepam—but there had been 16 deaths from meprobamate in 720 reported cases of poisoning.[6]

In the first years after the clinical introduction of meprobamate there was considerable debate over the question of a physical withdrawal syndrome. A controlled double-blind study by Haizlip and Ewing[9] showed a withdrawal syndrome in 44 of 77 patients suddenly deprived of the drug after 3.2 or 6.4 grams every day for 40 days. Insomnia, vomiting, tremors, muscle twitches, anxiety, headache and ataxia developed in 30 of them. Three of them had from one to three convulsions within 36 to 48 hours. Psychotic behavior, at times resembling delirium tremens, developed in eight of the patients, but persisted no longer than three days despite lack of specific treatment. Other observers have rarely found a withdrawal syndrome in patients who received a median dose of 1.6 grams every day for an average of four months. Goodman and Gilman[8] recommend that meprobamate dosage not exceed 2.4 grams daily.

I agree with Dr. Braun that Mrs. Hull's seizure and subsequent confused behavior were related to withdrawal of the meprobamate. Because people addicted to hypnotic drugs typically give unreliable drug histories, the so-called pentobarbital intoxication test has become fairly common. In short, one observes the patient's tolerance to increasing doses of pentobarbital, estimates the 24-hour dose needed to maintain intoxication and then gradually withdraws the drug—at the rate of about 10 percent a day. There is cross-dependence among the various central nervous system depressant drugs, and pentobarbital—or more recently phenobarbital—is a commonly used withdrawal agent. The therapeutic blood level for meprobamate is 1 mg per 100 ml, and 6 to 10 mg per 100 ml is generally associated with coma. In Mrs. Hull's the blood level of 4.2 mg per 100 ml probably affected her driving and gives a clue to the severity of her addiction.

DR. GERNER:* Some important points come up here. This lady apparently did have a severe depression, and I am thinking that she may have been misdiagnosed initially. Regardless of her case, however, I wonder if misdiagnosing and mistreating psychiatric disorders might not someday come into the same category as misdiagnosing and mistreating things like ulcers, appendicitis or brain tumors, and whether or not more consideration should be given to this by nonspecialists. Perhaps those patients whom practitioners treat chronically without finding the causes of their problems should be referred to a specialist. It seems to me that some drugs probably should not be allowed on the general market, or if they are they should be allowed to be prescribed only by certain physicians. For example, 5-fluorouracil is given only by specialists and only in certain situations. Yet other potentially dangerous drugs like glutethimide and meprobamate are dispensed almost indiscriminately. Only two drugs are really good for sleep, chloral hydrate and fluorazepam hydrochloride; the rest, although often prescribed for insomnia, destroy sleep insofar as we can measure. I wonder whether these potentially dangerous drugs (perhaps not chlordiazepoxide or diazepam because they are relatively safe) should be prescribed by doctors who are not specializing in the health of the mind and the emotions.

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DR. MORRISON: One of the most common misdiagnoses is to mistake anxiety neurosis for depression or vice versa. Very often when patients have moderate depression we see only the anxiety and do not look underneath it for the depression. This woman is an excellent case in point. She apparently had some depressive symptoms for at least ten years, which became notably worse during the six months preceding this admission.

DR. HUEY:* *What about an involutional depression?*

DR. MORRISON: The phrase involutional melancholia pretty much went out with insulin coma treatment; many patients who have primary affective disorder show up for the first time during the involutional period with depression, but there is nothing particularly different about them with regard to family history, response to treatment, and so on.

DR. BRAUN: I do think that Mrs. Hull's tubal ligation represented a significant loss for her, and the family corroborates that her symptoms became noticeable about that time.

DR. NEMIROFF:† I would like to address Dr. Braun's question about where to go from here. I think it would be dangerous at this point to decide that this woman is over her problem, in view of her addiction and her apparently lifelong problem with dependency needs. She still needs support and someone to work with, yet she is becoming resistant to continuing therapy. I suggest confronting her gently with her dependency needs and the way she handles them to see if that would encourage her to continue follow-up psychotherapy and give you the opportunity to monitor her antidepressant medication for a while longer. I think it would be a mistake to cut off that medication prematurely.

DR. BRAUN: Yes, and I think that continuing the marital therapy is also of paramount importance. I have advised the Hulls to get that kind of help nearer home; they have too much of an excuse not to get it here because of the distance. Unfortunately, Mr. Hull is not amenable to further counseling.

DR. HUEY: *How do you think her coming to this grand rounds is going to affect your relationship with her in ongoing therapy?*

DR. BRAUN: We have been working with this for two months; it was not something that I sprang on her last week. She perceives it as something she wanted to do for me, much as she does things for other people.

DR. MORRISON: In retrospect, then, we have a patient who may have been treated more or less appropriately with minor tranquilizers, according to the original diagnosis, but the results in this case were disastrous. Her abuse of meprobamate along with her anxiety apparently masked an underlying affective disorder. Withdrawal of the medication led to a convulsion which may have in fact partially "treated" her affective disorder, leaving her in an almost hypomanic state. She was finally treated with antidepressant medication, and today she appears to be much better.

Usually in the neuroses or psychiatric illnesses like schizophrenia or personality disorder we do not expect to see dramatic personality changes, although there may be accentuation of previously existing traits. When confronted with a patient who exhibits sudden personality change as Mrs. Hull did, we need to look for a tumor or other organic causes, for affective disorder (in which the changes are easily recognized by the family and by the patient) and of course for the abuse of alcohol or some other substance.

This woman does present a problem in differential diagnosis. Does she have anxiety neurosis with a secondary depression, or does she have an illness more closely allied with the affective disorders, with episodic attacks of anxiety as part of that? We cannot be sure. Woodruff[3] noted that in patients in whom both conditions developed, there was essentially no difference in the phenomena of their illnesses. He did not feel that it was important to distinguish between patients with and patients without affective disorder. I think, however, that in determining treatment we have to look for the depression, and if we find it we have to treat it—as Dr. Braun has done.

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REFERENCES

1. Lader MH (Ed): Royal Medico-Psychological Assoc Studies in Anxiety. Ashford Kent, World Psychiat Assoc and Headley Bros Ltd, 1969
2. Wheeler EO, White PD, Reed ER, et al: Neurocirculatory asthenia, anxiety neurosis, effort syndrome, neurasthenia. JAMA 142:878-888, 1950
3. Woodruff RA Jr, Guze SB, Clayton PJ: Anxiety neurosis among psychiatric outpatients. Compr Psychiat 13:165-170, 1972
4. Winokur G, Holeman E: Chronic anxiety neurosis: Clinical and sexual aspects. Acta Psych Scand 39:384-412, 1963
5. Slater E, Cowie V: The Genetics of Mental Disorders. London, Oxford Univ Press, 1971
6. Greenblatt DJ, Shader RI: Meprobamate: A study of irrational drug use. Am J Psychiat 127:1297-1303, 1971
7. Weatherall M: Tranquilizers. Br Med J 1:1219-1224, 1962
8. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. New York, The Macmillan Co., 1970
9. Haizlip TM, Ewing JA: Meprobamate habituation. N Engl J Med 258:1181-1186, 1958